AF/ 1616

PTO/SB/21 (08/03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/086,637
Filing Dater	March 4, 2002
First Named Inventor	Milton David GOLDENBERG
Art Unit.	1616
Examiner Name	HARTLEY, Michael G.
Total Number of Pages in This Submission	Attorney Docket No. 40923-0126 US3 [1094]

ENCLOSURES (Check all that apply)

- ☒ Fee Transmittal Form
  - ☒ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 (CFR) 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)_____
- ☐ After Allowance communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s), please identify below):

Remarks

Customer No. 26633

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	Patricia D. Granados, Reg. No.33,683, HELLER EHRMAN LLP
Signature	Patricia D. Granados
Date	May 9, 2005

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Effective 12/08/2004. Patent fees are subject to annual revision.

PTO/SB/17 (12-04) (Revised) (For payment of 37 CFR 1.17 fees including (f), (g), (h), & (i))

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 250.00

Complete if Known	
Application Number	10/086,637
Filing Date	March 4, 2002
First Named Inventor	Milton David GOLDENBERG
Examiner Name	Michael G. HARTLEY
Art Unit	1616
Attorney Docket No.	40923-0126 US3 [1094]

OIPE JC98 MAY 09 2005 PATENT & TRADEMARK OFFICE

METHOD OF PAYMENT (check one)

☒ Check	☐ Credit card	☐ Money Order	☐ Other	☐ None
☐ Deposit Account				

Deposit Account Number: 08-1641

Deposit Account Name: Heller Ehrman LLP

The Commissioner is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below

☒ Credit any overpayments and charge any deficiencies

☐ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the deposit account

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Entity Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Entity Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Entity Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	135	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

SUBTOTAL (1) $

2. EXTRA CLAIM FEES

Entity Fee ($)	Small Entity Fee ($)	Fee Description
50	25	Each claim in excess of 20 or, for Reissues, each claim in excess of 20 and more than in the original patent
200	100	Each Independent claim in excess of 3 or, for Reissues, each independent claim more than in the original patent
360	180	Multiple dependent claim, if not already paid

	Extra Claims		Fee from above		Fee Paid
Total Claims		-20** =		x	=
Independent Claims		-3** =		x	=

***or number previously paid, if greater; For Reissues see below*

Multiple Dependent =

SUBTOTAL (2) $

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof (round up to a whole number). See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s)

Total Sheets		Extra Sheets		Number of each additional 50	Fee ($)		Small Entity Fee ($)
	-100 =		/50 =		x 250	OR	x 125

SUBTOTAL (3) $

FEE CALCULATION (continued)

4. PETITION FEES UNDER 37 CFR 1.17 (f) — Fee Paid

Fee Code: 1462 **Fee $ 400** For petitions filed under: § 1.53(e); § 1.57(a); § 1.182; § 1.183; § 1.378(e); § 1.741(b)

5. PETITION FEES UNDER 37 CFR 1.17 (g) — Fee Paid

Fee Code: 1463 **Fee $ 200** For petitions filed under: § 1.12; § 1.14; § 1.47; § 1.59; § 1.103(a); § 1.136(b); § 1.295; § 1.296; § 1.377; § 1.550(c); § 1.956; § 5.12; § 5.15; § 5.25

6. PETITION FEES UNDER 37 CFR 1.17 (h) — Fee Paid

Fee Code: 1464 **Fee $ 130** For petitions filed under: § 1.19(g); § 1.84; § 1.91; § 1.102(d); § 1.138(c); § 1.313; § 1.314

7. PROCESSING FEES UNDER 37 CFR 1.17 (i) — Fee Paid

Fee Code: 1808 (1803 for § 1.221) **Fee $ 130** For petitions filed under: § 1.28(c)(3); § 1.41; § 1.48; § 1.52(d); § 1.53(b)(3); § 1.55; § 1.99(e); § 1.103(b); § 1.103(c); § 1.103(d); § 1.217; § 1.221; § 1.291(c)(5); § 1.497(d); § 3.81

8. OTHER FEES

Entity Fee ($)	Entity Fee ($)	Fee Description	Fee Paid
130	65	Surcharge - late filing fee or oath	
50	25	Surcharge - late provisional filing fee or cover sheet	
130	130	Non-English specification	
2,520	2,520	For filing a request for *ex parte* reexamination	
920*	920*	Requesting publication of SIR prior to Examiner action	
1,840*	1,840*	Requesting publication of SIR after Examiner action	
120	60	Extension for reply within first month	
450	225	Extension for reply within second month	
1,020	510	Extension for reply within third month	
1,590	795	Extension for reply within fourth month	
2,160	1,080	Extension for reply within fifth month	
500	250	Filing a brief in support of an appeal	250.00
790	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1,510	1,510	Petition to institute a public use proceeding	
500	250	Petition to revive - unavoidably abandoned application	
1,500	750	Petition to revive - unintentionally abandoned application	
50	50	Processing fee for provisional appls (37 CFR 1.17(q))	
180	180	Submission of Information Disclosure Statement	
1,000	500	Request for oral hearing	
790	395	For each additional invention to be examined (37 CFR 1.129(b))	
790	395	Request for Continued Examination (RCE)	
900	900	Request for expedited examination of a design application	

Other fee (specify)

SUBTOTAL (4+5+6+7+8) $ 250.00

* Reduced by Basic Filing Fee Paid

SUBMITTED BY

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Signature	Patricia D. Granados	Date	May 9, 2005	Customer No.	26633

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Attorney Docket No.: 40923-0126 US3 [1094]
(18733-1094)

In re patent application of:
Milton D. Goldenberg

Confirmation No.: 8273

Application No.: 10/086,637

Art Unit: 1616

Filing Date: March 4, 2002

Examiner: Michael G. Hartley

For: Intraoperative Intravascular And Endoscopic Tumor And Lesion Detection, Biopsy And Therapy.

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Heller Ehrman LLP

APPEAL BRIEF

I. REAL PARTY IN INTEREST

Immunomedics, Inc. of 300 American Road, Morris Plains, NJ 07950 as assignee, owns the entire right, title and interest in the captioned application and, therefore, is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other current appeals, interferences or judicial proceedings which may be related to, directly affect or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 99-201 are pending; claims 99-182, 194,195 and 198-201 are withdrawn from consideration; and claims 183-193, 196 and 197 stand finally rejected and are under appeal. A copy of the claims on appeal are appended to this brief.

Claims 1-98 have been canceled without prejudice or disclaimer.

IV. STATUS OF AMENDMENTS

All amendments of record have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is directed to a method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:

(a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less[1], wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;

(b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and

(c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.[2] The antigen in the above described method may be produced or associated with a lesion is a tumor- or pathogen-associated antigen.[3]

The above method may further comprise after step (a), the step of injecting the patient with a clearing composition comprising an agent to clear circulating

[1] Specification at page 13, line 33 to page 14, line 2.

[2] Specification at page 11, line 38 to page 12, line 24.

[3] Specification at page 14, lines 3 to 7.

bispecific antibody.[4] The clearing composition may comprise an anti-idiotype antibody and such anti-idiotype antibody may be conjugated to a galactosyl residue.[5]

The above method may further comprise the step of removing lesions at sites of elevated label accretion with a laser therapy, brachytherapy, chemo immunotherapy, radioimmunotherapy, photodynamic therapy, external beam irradiation or surgical removal.[6] According to the invention, lesions at sites of elevated label accretion may be treated with ionizing radiation.[7] Such lesions may be a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.[8] In one embodiment, the method is a laparscopic procedure.[9]

In the method of the invention, the hapten may be labeled with a diagnostic radioisotope, a MRI image enhancing agent or a fluorescent label.[10]

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[4] Specification at page 12, lines 12-15.

[5] *Id.*

[6] Specification at page 8, line 1 to page 9, line 2; page 11, lines 15 to 23.; and page 22, lines 30-35.

[7] Specification at page 11, lines 15 to 23.

[8] Specification at page 13, lines 4 to 12.

[9] Specification at page 23, lines 2-3.

[10] Specification at page 12, lines 14-20.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 183,187-189,191-193 and 197 stand rejected under 35 USC § 103 (a) as being obvious over Goldenberg (U.S. Patent No. 4,932,412) ("Goldenberg") in view of Barbet (U.S. Patent No. 5,256,395) ("Barbet").

2. Claim 190 stands rejected under 35 USC § 103 (a) as being obvious over Goldenberg in view of Barbet in further view of Horowitz (U.S. Patent No. 4,706,652) ("Horowitz").

VII. ARGUMENT

A. The Invention of Claims 183, 187-189, 191-193, 196 and 197 Would Not Have Been Obvious Over Goldenberg in View of Barbet.

1. The Law

The law requires the Examiner, when combining references to make out a *prima facie* case of obviousness, to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that it is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43. Thus, the Examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

Additionally, it is impermissible within the framework of 35 USC § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of the parts necessary for the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F. 2d 443, 230 USPQ. 416 (Fed. Cir. 1986).

2. The Examiner's Case

The Examiner's rejection is straightforward: Goldenberg teaches everything recited in claim 183 except the use of a labeled hapten/bispecific antibody system for targeting the radioimmunopharmaceuticals; Barbet teaches the missing element and provides the motivation to combine the teachings of Goldenberg and Barbet by suggesting that a labeled hapten/bispecific antibody system would improve the same type of methods taught by Goldenberg. Office Action of December 8, 2004, page 3, third paragraph.

3. What's Wrong with the Examiner's Case

a. Wrong as a Matter of Fact

The first problem with the Examiner's case is that Goldenberg does not teach what the Examiner says it does; Goldenberg does not teach all the elements of the claimed invention except the hapten system. Goldenberg fails to disclose other elements as well and is directed to a process that is essentially different from what is presently being claimed. In fact, the only thing that Goldenberg and the invention of claim 183 have in common is what is recited in the preamble of claim 183: a method of close-range detection of lesions during a procedure. All of the elements defining the steps of the method are different. Claim 183 is as follows:

> 183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:
>
> (a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular

> weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;
>
> (b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and
>
> (c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.

Step (a) requires a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less. Goldenberg nowhere directs the skilled artisan toward such a molecule. Although Goldenberg teaches a primary antibody that is labeled and that targets a tumor antigen, Goldenberg's invention isn't concerned with this step; it is concerned with a subsequent step, which is a method of reducing background radiation so as to obtain an accurate reading of the radiation associated with the primary antibody that binds the tumor antigen. Goldenberg states that the primary antibody could be any type of antibody. It states:

> The antibody used as the primary imaging antibody in the method of the present invention may be whole IgG, IgA, IgD, IgE, IgM and the like or a fragment such as e.g., F(ab')2, F(ab)2, Fab, Fab or the like, including isotypes and subtypes thereof. It can be a polyclonal antibody, preferably an affinity-purified antibody from a human or an appropriate animal, e.g. a primate, goat , rabbit, mouse or the like, or a monoclonal antibody prepared by conventional techniques, e.g., a murine antibody derived from a hybridoma produced by fusion or lymph or spleen cells from a mouse immunized against a cancer hybridoma produced by fusion of lymph or spleen cells from a mouse immunized against a cancer antigen with myeloma cells from an

> appropriate immortal cell line. It will be appreciated that newer techniques for production of monoclonals can also be used, e.g. human monoclonals, interspecies monoclonals, chimeric (e.g human/mouse) monoclonals, genetically engineered antibodies and the like.
>
> It should be noted that mixtures of antibodies, isotypes, and immunoglobulin classes, including fragments can be used, as can hybrid antibodies and/or antibody fragments. The hybrids can have two different antigen specificities, e.g. one arm binding to another antigen, e.g., CSAp. Or one arm could bind to one epitope on, e.g., CEA and the other arm could bind to another CEA epitope. The foregoing are merely illustrative, and other combinations of specificities can be envisioned that also fall within the scope of the invention. Hybrid antibody fragments with dual specificities can be prepared analogously to the anti-tumor marker hybrids disclose in U.S. Pat. No. 4,361,544. Other techniques for preparing hybrid antibodies are disclosed in, e.g., U.S. Pat. Nos. 4,474,893 and 4,479,895 and in Milstein et al., Immunol. Today, 5, 299 (1984).

Column 6, line 50 to column 7, line 15. The above describes a large universe of possible primary antibodies. This is true because in order to practice the Goldenberg invention, it doesn't really matter what type of antibody is used as the primary antibody. The nature of the primary antibody is simply not relevant to Goldenberg's invention. Accordingly, Goldenberg doesn't direct the reader to any particular type of antibody, and clearly does not mandate the use of a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less.

On the other hand, the type and size of antibody is relevant to the invention of claim 183. The specification describes the preferred antibodies and explains why such antibodies are preferred. For instance, bivalent antibodies have better targeting and affinity for antigens than monovalent antibodies. (Specification at

page 26, lines 7-28.) Moreover, smaller antibodies are critical for rapid clearance and step (c) of claim 183 introduces a time limit for such clearance. The present specification explains these things below:

> A $F(ab)_2$ or $F(Ab')_2$ fragment is too large to be filtered through the golmerular basal membrane. This divalent fragment must be catabolized elsewhere; e.g. in the liver, and the smaller breakdown products are excreted via the kidneys. Without the use of a clearing agent, the clearance of this fragment takes longer than the divalent single chain fragments of the present invention and can unduly delay other procedures.
>
> The divalent single chain antibody fragment or subfragments useful in the present invention have a molecular weight of 85,000 daltons or less, which is about the upper limit for filtration by the kidneys. The molecular weight of these antibody fragments can be 65,000 daltons or less, 55,000 daltons or less or 50,000 daltons or less....

Specification at page 26, line 29 to page 27, line 4.

Goldenberg does not guide the reader toward this type and size of antibody because Goldenberg's method does not rely upon the advantages gained from using a bispecific single chain antibody fragment or subfragment that is 85,000 daltons or less. Rather, Goldenberg's method reduces non-specific background radiation by either using a contrast or subtraction agent or by administering a second antibody that binds the primary antibody that is in circulation or by using the contrast/subtraction agent and the second antibody. Thus, contrary to the Examiner's conclusion, step (a) is neither taught nor suggested by Goldenberg.

Step (b) of claim 183, requires the administration of a bivalent hapten that quickly localizes at the target site and clears through the kidneys. The Examiner

admits this is not taught or suggested by Goldenberg. This is why the Examiner cites Barbet.

Step (c) of claim 183 recites detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure. The Examiner has argued in the Office Action of June 1, 2004 at page 4, second paragraph, that Goldenberg teaches (at column 2, lines 5-54) "detecting the presence of elevated levels of accreted labels at the target site within 48 hours of said procedure." Appellants agree that part (c) of claim 183 recites "48 hours," that Goldenberg describes a 2-72 hour time range and that the number 48 falls within the range of 2 to 72. However, part (c) of claim 183 must be read in its entirety. Part (c) reads "within 48 hours of the first injection." The 2-72 hour range discussed in Goldenberg pertains to something else. It pertains to the time it takes after the injection of a second antibody for such second antibody to clear a certain percentage of the primary antibody, which is not bound to a target antigen but which is in circulation. Respectfully, by reading neither claim 183 nor Goldenberg in its entirety, the Examiner is comparing apples with oranges.

Specifically, Goldenberg teaches that the proper time for conducting "the procedure" is when the level of background radiation is sufficiently reduced. Specifically, Goldenberg teaches that the "localization ratio" of the labeled primary antibody in tumor tissue increases by at least about 20%, preferably at least about 50% within 2 to 72 hours following injection of the second antibody. The localization ratio is the ratio of target to non-target activity of the radionuclide

used to label the primary antibody (Column 12, line 58 to column 13, line 4): the higher the ratio the greater the reduction in background radiation. Goldenberg explains that it is important to take blood samples at periodic intervals after administration of the second antibody to monitor the level of the primary antibody label in the blood. The time to perform the desired procedure is when the level of circulating primary antibody label is reduced by 75%, preferably 85% or more. (Column 13, lines 17 to 34).

It is clear from the above that the 2-72 hour range discussed in Goldenberg is not related to the period of time following the first injection as is required by part (c) of claim 183; it is related to the period of time following the second injection. Goldenberg does not say what amount of time elapses between the first injection and second injection. In fact, Goldenberg is more concerned with percentages of clearance (localization ratios) than the rapidity of clearance. In one embodiment, Goldenberg suggests multiple injections of a second antibody so as to ensure proper clearance. (Column 13, lines 26-28). Thus, the Examiner's conclusion that Goldenberg teaches step (c) of claim 183, which requires the procedure be conducted within 48 hours of the first injection, is wrong as a matter of fact.

Goldenberg simply is not the template for obviousness the Examiner believes it is. One of skill in the art reading Goldenberg and Barbet would not have been directed to the present invention. Goldenberg teaches a method that is substantially different from the invention of claim 183, as demonstrated by the above element - by - element analysis. The fact that Barbet teaches using haptens for radioimmunotherapy and detection does not cure the deficiencies in Goldenberg. It appears that the Examiner has simply read the preamble to one

of Goldenberg's claims and assumed that if one used a hapten in Goldenberg's method, one would arrive at the claimed invention and this would have been an obvious choice because Barbet suggests the use of haptens for radioimmunotherapy. This ignores all of what Goldenberg actually teaches and, more importantly, ignores the elements recited in claim 183.

b. Wrong as a Matter of Law

The Examiner's position is insupportable as a matter of law because it is based upon a selective reading of Goldenberg. Contrary to the Examiner's protests (Final Office Action of December 8, 2004, page 3, second and third paragraphs.) the Examiner, in fact, has picked and chosen from Goldenberg only what supports his position. And, in doing so, the Examiner has not always been accurate in comparing Goldenberg's teachings with the specific steps recited in claim 183. Although the Examiner may properly have characterized Barbet as teaching haptens and the desirability of using haptens in radioimmunotherapeutic methods, the method of claim 183 is more than what is recited in the preamble. It is a specific method having three steps that are not suggested by Goldenberg when accurately and completely read by one of skill in the art. Consequently, even if one were motivated to combine Barbet with Goldenberg, one would not arrive at the presently claimed invention.

B. Claim 190 would not have been obvious over Goldenberg in view of Barbet in further view of Horowitz (U.S. Patent No. 4,706,652) ("Horowitz").

Claim 190 is rejected as obvious over Goldenberg in view of Barbet in further view of Horowitz (U.S. Patent No. 4,706,652) ("Horowitz"). Claim 190

depends from claim 183 and recites that the method further comprises the step of administering brachytherapy via the endoscope or catheter to lesions at sites of elevated label secretion. The Examiner cites Horowitz for teaching that brachytherapy, by administering radioactive seeds via a catheter, provides the advantage of safer implants that allow the patient to be discharged.

Appellants rely upon the above arguments with regard to Goldenberg and Barbet to address the rejection of claim 190. Horowitz does not cure the deficiencies in the Examiner's case with regard to the primary references.

C. Double Patenting

In the Final Office Action, the Examiner has maintained the double patenting rejection of claims 183-193, 196 and 197 over claims 1-9 of U.S. Patent No. 6,387,350. Appellants will file a terminal disclaimer upon remand to the Examiner with the reversal of the outstanding prior art rejections.

* * *

In view of the above arguments and evidence of record, Appellants respectfully request the Board to reverse the Examiner's rejection of claims.

Respectfully submitted,

May 9, 2005

Patricia D. Granados
Reg. No. 33,683

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Heller Ehrman LLP

VII. CLAIMS APPENDIX

183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:

(a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;

(b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and

(c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.

184. The method of claim 183, further comprising after step (a), the step of injecting said patient with a clearing composition comprising an agent to clear circulating said bispecific antibody.

185. The method of claim 184, wherein said clearing composition comprises an anti-idiotype antibody.

186. The method of claim 185, wherein said anti-idiotype antibody is conjugated to a galactosyl residue.

187. The method of claim 183, wherein said antigen produced or associated with a lesion is a tumor- or pathogen-associated antigen.

188. The method of claim 183, further comprising the step of removing lesions at sites of elevated label accretion with a laser therapy, brachytherapy, chemo immunotherapy, radio immunotherapy, photodynamic therapy, external beam irradiation or surgical removal.

189. The method of claim 183, further comprising the step of treating lesions at sites of elevated label accretion with ionizing radiation.

190. The method of claim 183, wherein the procedure is selected from the group consisting of an endoscope, laparoscope, and intravascular catheter procedures, further comprising the step of administering brachytherapy via the endoscope or catheter to lesions at sites of elevated label accretion.

191. The method of claim 183, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

192. The method of claim 183, wherein said procedure is a laparoscopic procedure.

193. The method of claim 183, wherein said hapten is labeled with a diagnostic radioisotope, a MRI image enhancing agent or a fluorescent label.

IX. EVIDENCE APPENDIX

The following is a list of references entered by the Examiner and/or relied upon by Appellant in this appeal, along with a statement setting forth where in the record that evidence was entered by the examiner and/or the appellant. Copies of each piece of evidence are provided herewith.

Reference	Location in the Record
1. U.S. Patent No. 4,932,412 ("Goldenberg")	Office Action of June 1, 2004, page 4, first paragraph; Response of November 1, 2004, page 18-21; Final Office Action of December 8, 2004, pages 2-4.
2. U.S. Patent No. 5,256,395 ("Barbet")	Office Action of June 1, 2004, page 4, first paragraph; Response of November 1, 2004, page 18-21; Final Office Action of December 8, 2004, pages 2-4.
3. U.S. Patent No. 4,706,652 ("Horowitz")	Office Action of June 1, 2004, page 4, first paragraph; Response of November 1, 2004, page 18-21; Final Office Action of December 8, 2004, pages 2-4.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.